REMARKS/ARGUMENTS

Upon entry of the present amendment, claims 6, 8, 19, 25, 31 and 36-42 are pending and presented for examination. Claims 1-5, 7, 9-18, 20-24, 26-30 and 32-35 have been canceled without prejudice or disclaimer. Claims 6, 8, 19, 25, 31, 36, 38 and 40 have been amended. Claim 42 is newly added. The Examiner has indicted that claims 37, 39 and 41 contain allowable subject matter.

Support for the amendments to claims 6, 19, 25 and 31 is found, *inter alia*, in the claims and compounds as originally filed. Additional support for the amendment to claims 6, 8 and 19 is found, *inter alia*, on page 11, lines 26-29, and on page 12, lines 11-19. Support for the amendment to claims 36, 38 and 40 and new claim 42 is found, *inter alia*, in Figures 2A-B of the present application. As such, Applicants believe no new matter is present in this or any other portion of the present amendment.

Reconsideration of the application is respectfully requested in view of the above amendments to the claims and the following remarks. For the Examiner's convenience and reference, Applicants' remarks are presented in the order in which the corresponding issues were raised in the Office Action.

I. INTRODUCTION

The present invention provides, *inter alia,* compounds, pharmaceutical compositions and methods of using the compounds for the treatment of FXR-mediated conditions and disorders as well as the modulation of *cyp*7a expression levels in mammals. FXR-mediated conditions and disorders include, for example, atherosclerosis, peripheral vascular disease, cardiovascular disease, hypercholesteremia, cholesterolemia, obesity, diabetes, and inflammatory conditions and diseases associated with abnormally high or low cholesterol levels.

II. IMPROPER MARKUSH REJECTION

The Examiner rejected claims 6, 8, 9, 25, 31, 36, 38 and 40 as allegedly being of improper Markush format in the definitions of A^3, X and A^2. Applicants believe that the Examiner's rejection of claim 9 may be a typographical error as claim 9 is drawn to the non-elected invention (Group II). The Examiner may have intended to reject claim 19, which is part of the elected group. In any event, the Examiner alleges the resulting compounds defined by the claims are structurally diverse and patentably distinct from each other. The Examiner has suggested that amending the claims to aryl amides, which encompass the elected species, will overcome the rejection.

In order to expedite prosecution of the present application, Applicants have incorporated the Examiner's suggestions. The compound and composition claims have been amended to encompass the aryl amides of the present invention. Claims 36, 38, 40 and 42 are drawn to certain preferred species of present invention.

Applicants respectfully point out that Applicants' method claims are broader in scope than their compound and composition claims. As explained more fully below, the cited art does not teach or suggest FXR modulation nor does it teach or suggest modulating *cyp*7a expression levels in a mammal. Again, Applicants submit that the claims are definite and the Markush groups share a common structural feature. Accordingly, Applicants respectfully request that the rejection of claims 6, 8, 25, 31, and 36 be withdrawn.

III. REJECTION UNDER 35 U.S.C. § 112

The Examiner has rejected claims 38 and 40 as allegedly being indefinite. The Examiner alleges that making a reference to the drawings for the intended compounds renders the claims indefinite and suggests inclusion of the intended structural formulas in the claims directly. In response, Applicants have followed the Examiner's suggestion and inserted the chemical formulae directed into the claim. Therefore, Applicants respectfully request that the Examiner withdraw the rejection.

IV. REJECTION UNDER 35 U.S.C § 103

The Examiner has rejected claims 6, 8 and 19 under 35 U.S.C. 103(a) as allegedly being obvious over Baldwin *et al.* (U.S. Patent No. 4,279,887), Kawada *et al.* (U.S. Patent No. 4,123,554), Chiyomaru *et al.* (U.S. Patent No. 3,985,804), or Schwartz *et al*, (U.S. Patent No. 3,407,056). The Examiner alleges that the present product claims, in addition to encompassing an unsubstituted N-phenylbenzamide, also encompass the species in the cited art. The Examiner alleges that one would be motivated to prepare the present compounds from within the genus of the references with the expectation of obtaining additional useful compounds. To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

As set forth in M.P.E.P. § 2143:

> [t]o establish a *prima facie* case of obviousness, *three* basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

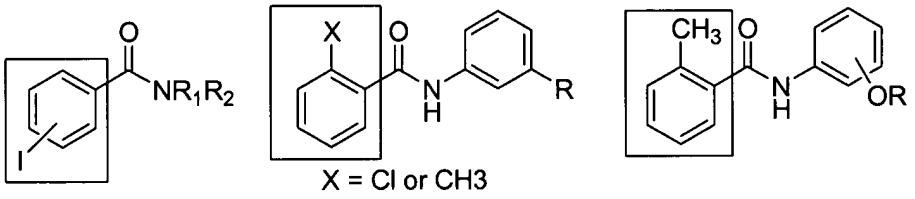
All three elements set forth above must be present in order to establish a *prima facie* case of obviousness. Applicants assert that a *prima facie* case of obviousness has not been established for the following reasons: 1) there is no suggestion or motivation to modify the references; 2) there is no reasonable expectation of success; and 3) the cited art references do not teach or suggest all the claim limitations.

A. There is No Suggestion or Motivation to Modify the References

Applicants state that there is simply no motivation or suggestion provided in the cited references to modify their teaching in the way the Examiner has contemplated. Obviousness can only be established by combining or modifying the teachings of the cited art

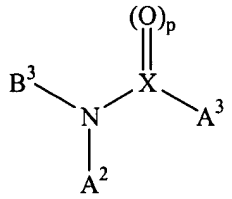
to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

Baldwin *et al.*, Kawada *et al.*, and Chiyomaru *et al.*, teach compounds having a benzamide group in which the phenyl ring is **substituted** (*see*, boxed area below). In particular, Baldwin *et al.* teach that iodo-substituted benzamides can be used as brain imaging agents. Kawada *et al.* and Chiyomaru *et al.* teach 2-methyl or 2-chloro substituted benzamides as germicidal agents. Shown below are the generic structures corresponding to the invention of Baldwin *et al.*, Kawada *et al.*, and Chiyomaru *et al.*



Baldwin et al. Kawada et al. Chiyomaru et al.

In the compound and composition claims (claims 6 and 19 and dependent claims therefrom), Applicants teach *inter alia*, benzamide compounds in which the phenyl ring (A^3) on the benzamide is **unsubstituted** (*see*, Figure 2A). Claim 6 recites:

> **6.** (Amended) A compound of the formula
>
> 
>
>
> **II**
>
> wherein: A^3 is a member selected from the group consisting of alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, **unsubstituted aryl**, heteroaryl, arylalkyl, (heteroaryl)alkyl, aryl(heteroalkyl), and (heteroaryl)heteroalkyl;

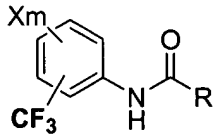
The above cited references simply do not teach or suggest making benzamides wherein the benzamide ring is **unsubstituted.** Rather, each cited reference clearly teaches

that the phenyl ring is substituted and the substitution on the phenyl ring is a critical feature of the invention.

Applicants teach in the method claims, an alkylene group (*e.g.*, a methylene) to the right of the carbonyl portion of the amide (*see*, for example, compounds 2.2.1 to 2.24 of Figures 2A-B). Again, this embodiment is not taught or suggested by the cited art.

Thus, one skilled in the art would not be motivated to make an unsubstituted benzamide compound or to add an alkylene group to the right of the carbonyl portion of the amide functionality of the present invention in view of the cited art because there is no incentive to do so.

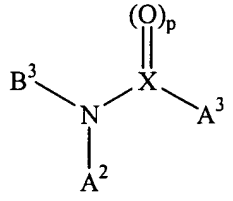
Moreover, Schwartz *et al.* teach that certain N-trifluoromethylphenyl benzamides are herbicidal agents. The generic structure of Schwartz *et al.* is shown below.



Schwartz et al.

In stark contrast, Applicants set forth in amended claims 6 and 19, a set of preferred substituents for the N-aryl group of the N-arylbenzamides which **are not** taught by Schwartz *et al.* Claim 6 recites:

6. A compound of the formula



II

wherein: A^2 is a substituted aryl group selected from the group consisting of substituted phenyl and substituted naphthyl;

wherein said substituted aryl group is substituted with 1-5 substituents selected from the group consisting of **hydroxy, -OR', -NH_2, -OC(O)R', -NR'R", -SR', -CN, -NO_2, -CO_2R', -CONR'R", -C(O)R', -OC(O)NR'R", -NR"C(O)R', -NR"$C(O)_2$R', -NR'-C(O)NR"R"', NH-$C(NH_2)$=NH, -NR'-**

$C(NH_2)=NH$, $-NH-C(NH_2)=NR'$, $-S(O)R'$, $-S(O)_2R'$, $-S(O)_2NR'R''$, $-NR''-S(O)_2-R'$, N_3, chloro, bromo, fluoro, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, and neopentyl;

Schwartz *et al.* simply does not teach or suggest Applicants' substituents on the N-aryl group. Instead, Schwartz *et al.* teaches the importance of a trifluoromethyl group in maintaining the desired herbicidal activity of the N-phenyl benzamide compounds. As set forth in Schwartz *et al.*:

> The compounds of Formula I are distinguished from the prior art halogenated anilides not only be [sic] chemical structure but also in their plant growth regulating activity. The trifluoromethylanilides of Formula I possess both pre-emergence and post-emergence activity while the prior art halogenated anilides possess only post-emergence activity which limits their application. In addition, the trifluoromethylanilides possess a different seelectivity [sic] in their herbicidal activity. col. 2, lines 47-55.

In view of Schwartz *et al.*, one skilled in the art would not be motivated to prepare N-arylbenzamides, wherein the aryl group was **not** substituted directly on the ring with a trifluoromethyl group, because the compounds which are herbicidally active possess a CF_3 group substituted **directly** on the ring. In view of the foregoing, Applicants respectfully request that the Examiner withdraw this rejection.

B. There is No Reasonable Expectation of Success

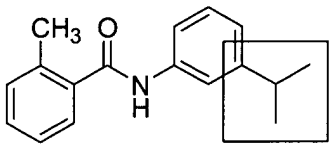
In addition, there is no reasonable expectation of success that the modification the Examiner contemplates will succeed. "Both the suggestion and the expectation of success must be found in the prior art, not the Applicants' disclosure." *In re Dow Chem. Co.*, 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988).

Baldwin *et al.*, Kawada *et al.*, Chiyomaru *et al.* and Schwartz *et al.* each teach benzamide compounds that have specific substituents (*i.e.*, halogen, methyl, iodo, trifluoromethyl) on either the phenyl ring of the benzamide group or on the N-aryl ring of an

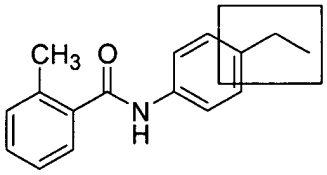
N-arylbenzamide. These compounds are taught to have brain imaging, germicidal, or herbicidal properties. There is absolutely no teaching or suggestion in the cited art that compounds that have substituents other than from what is taught will possess any biological (*e.g.*, FXR modulating) activity. Further, the cited art does not teach or suggest FXR modulation nor does it teach or suggest modulating *cyp*7a expression levels in a mammal.

In an illustrative example, Kawada *et al.* show, by way of comparative biological data between variously substituted N-phenylbenzamides, that maintenance of high germicidal activity requires that N-phenylbenzamide compounds possess a methyl group on the benzamide ring and an alkyl group at the meta position on the N-phenyl ring (*see*, Table 1, Kawada *et al.*). As such, Kawada *et al.* does not provide any motivation or suggestion for making compounds that divert from the rigid structural motif disclosed therein.

Germicidal Activity of Kawada et al.'s compounds:
Protection Value = % protection again infection by rice sheath blight as compared to untreated speciman.



Compound No. 13
Protection Value = 100%



Compound No. 114
Protection Value = 0%

Similar examples comparing biological activity are also found in Chiyomaru *et al.* (*see* column 9, Table 1, Compound 1 vs. Compound 26) and in Schwartz *et al.*, (*see* selectivity data in Table 5 as compared to selectivity profile of cited art compounds in column 1, lines 40-50). Moreover, since brain imaging agents are necessarily radioactive, there is no suggestion or motivation in Baldwin *et al.* to prepare compounds that lack a radioactive group such as a radioactive iodide atom.

Furthermore, given that the cited references only teach that the benzamides compounds are germicidal and herbicidal agents or function as brain imaging agents, there is simply no basis to expect that these compounds could also be used successfully for a completely unrelated purpose such as modulating the FXR receptor for the treatment of

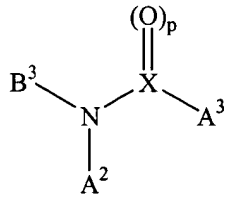
atherosclerosis. Applicants submit that there is simply no suggestion in the cited references that indicates that modification of the disclosed compounds will result in additional beneficial compounds. To the contrary, Applicants submit that the cited art teach that small modification of the disclosed genus will result in a significant decrease in the disclosed activity (*see*, Table 1, Kawada *et al.*). Thus, Applicants respectfully request that the Examiner withdraw the rejection.

C. The Cited Art References Do Not Teach All Limitations of the Claims

The prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). Applicants assert that the prior art references do not teach or suggest all the limitations of the claims and, therefore, the obviousness rejection is untenable.

Applicants teach N-arylbenzamide compounds and compositions in which the phenyl group of the benzamide is unsubstituted and the N-aryl ring is substituted with a preferred set of substitutents as set forth in claims 6 and 19:

6. A compound of the formula



II

wherein:

A^2 is a substituted aryl group selected from the group consisting of substituted phenyl and substituted naphthyl;

wherein said aryl group is substituted with 1-5 substituents selected from the group consisting of **hydroxy, -OR', -NH_2, -OC(O)R', -NR'R", -SR', -CN, -NO_2, -CO_2R', -CONR'R", -C(O)R', -OC(O)NR'R", -NR"C(O)R', -NR"$C(O)_2$R', -NR'-C(O)NR"R"', NH-$C(NH_2)$=NH, -NR'-$C(NH_2)$=NH, -NH-$C(NH_2)$=NR', -S(O)R', -$S(O)_2$R', -$S(O)_2$NR'R", -NR"-$S(O)_2$-R', N_3, chloro, bromo, fluoro, methyl, ethyl, propyl,**

isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, and neopentyl;

A^3 is a member selected from the group consisting of alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, **unsubstituted aryl**, heteroaryl, arylalkyl, (heteroaryl)alkyl, aryl(heteroalkyl), and (heteroaryl)heteroalkyl;

Applicants teach in the method embodiments, an alkylene group (*e.g.*, a methylene) to the right of the carbonyl portion of the amide (*see*, for example, 2.2.1 to 2.24 of Figures 2A-B). The cited art does not teach or suggest FXR modulation nor does it teach or suggest modulating *cyp*7a expression levels in a mammal.

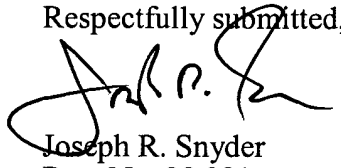
Applicants submit that Kawada *et al.*, Chiyomaru *et al.*, and Baldwin *et al.*, either alone or in combination, do not teach a benzamide group wherein the phenyl ring of the benzamide ring is **unsubstituted,** or an alkylene group (*e.g.*, a methylene) to the right of the carbonyl portion of the amide (*see*, for example, 2.2.1 to 2.24 of Figures 2A-B), as is presently taught and claimed. In addition, Schwartz *et al.* do not teach the substituents on the N-aryl group that are taught in the present invention. As such, it is clear that none of the cited art references teach Applicants' claimed invention. Therefore, Applicants respectfully submit that the instant claims are unobvious in view of the cited references and respectfully request that the rejection be withdrawn.

V. CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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